Recombinant Advisory Committee Meeting September 13, 2011

- Bone Marrow Transplantation for X-SCID Infants in the First 3.5 Months of Life at Duke University Medical Center

Rebecca H. Buckley, M.D.

Human Severe Combined Immunodeficiency (SCID)

A fatal syndrome of diverse genetic origin, characterized by absence of T and B cell (and sometimes NK cell) functions.

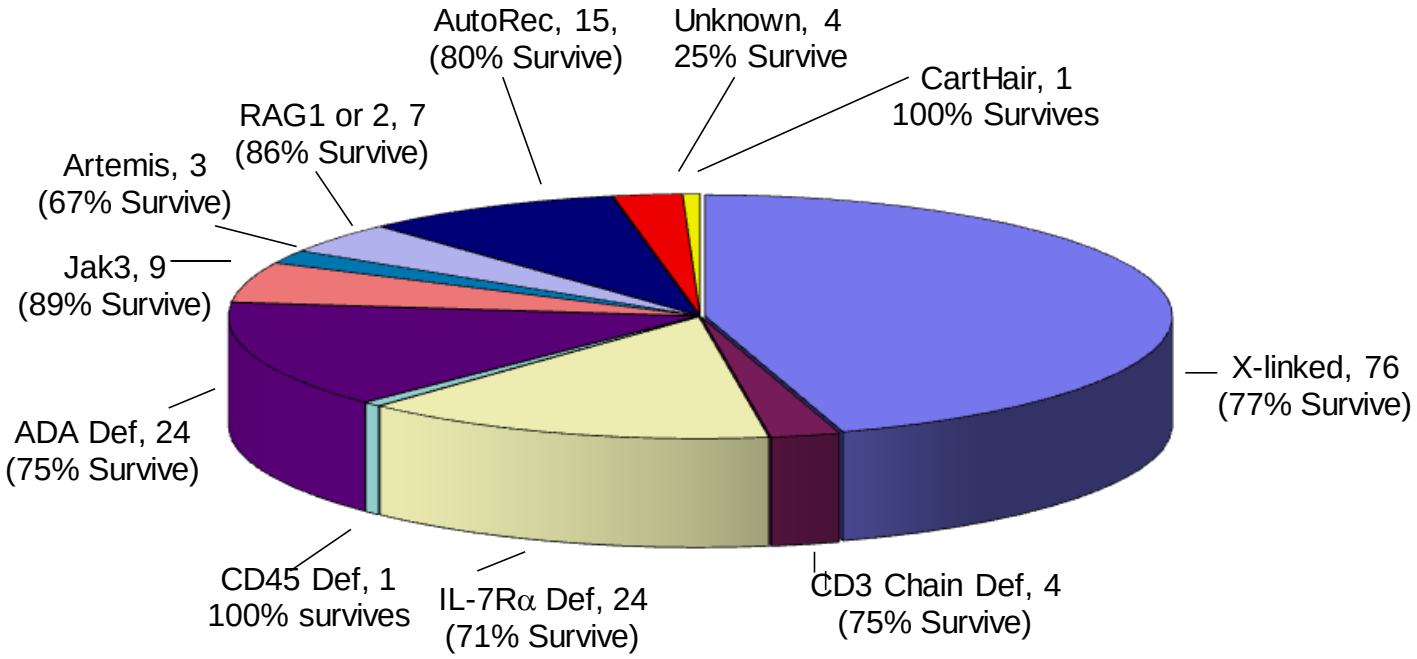
Thirteen Abnormal Genes in SCID

- Cytokine Receptor Genes
  - *IL2RG*
  - *JAK3*
  - *IL7Rα*
- Antigen Receptor Genes
  - *RAG1*
  - *RAG2*
  - *Artemis*
  - *Ligase 4*
  - *DNA-PKcs*
  - *CD3δ*
  - *CD3ε*
  - *CD3ζ*
- Other Genes
  - *ADA*
  - *CD45*

Bone Marrow Transplantation* for Severe Combined Immunodeficiency at Duke University Medical Center 5/19/82-9/13/11

- Number surviving: 128 of 168 or 76%.
- Survivors range from 2 months to 29.4 years post-transplantation.
- HLA-identical: 17 of 17 or 100%.
- HLA haploidentical: 111 of 151 or 74%.
- When transplanted before 3.5 months of life, 45/48 (94%) survive up to 29.4 years. Survival rate only 69% for those transplanted after 3.5 months of life.

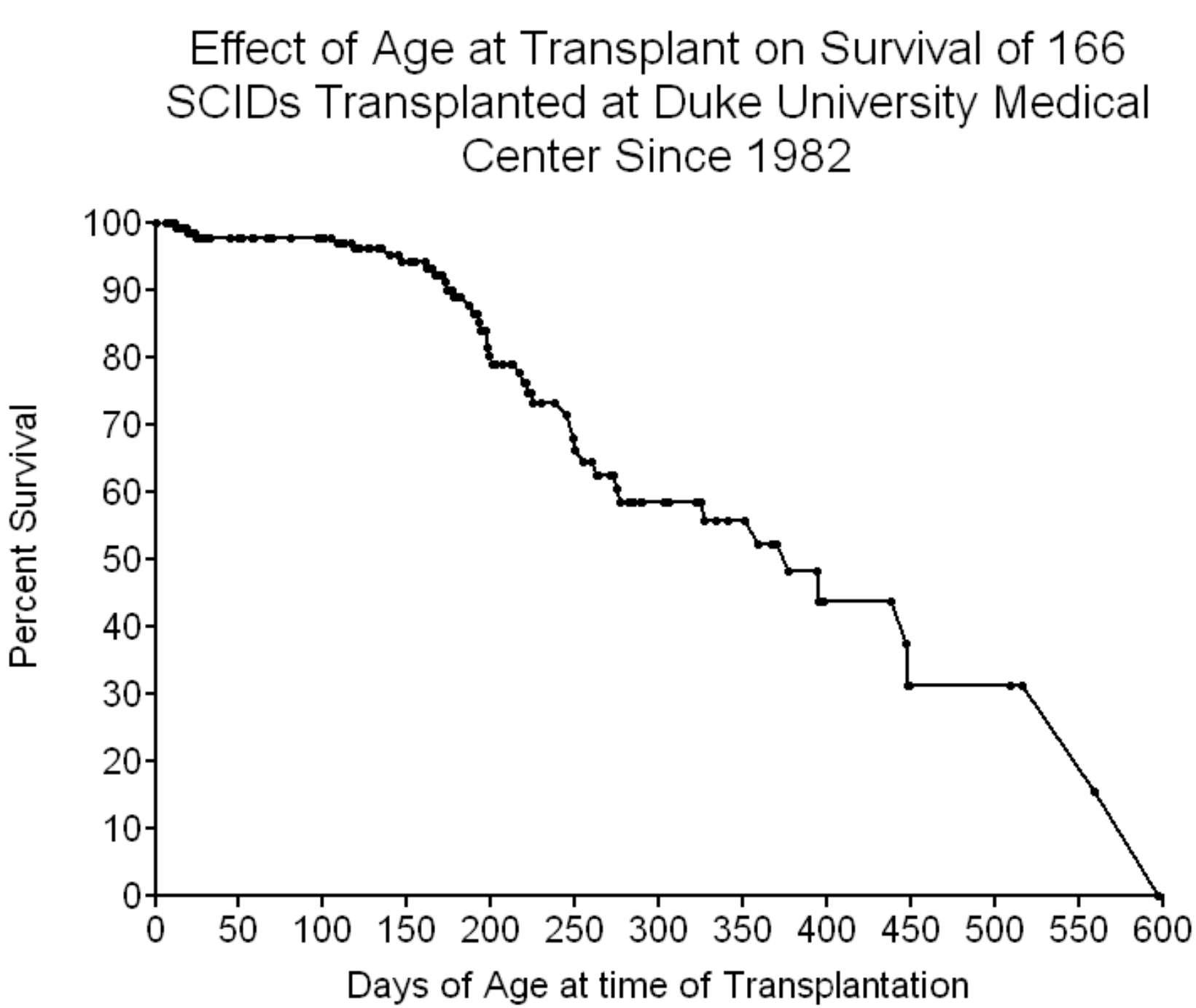
* Non-ablated; related donors.



Survival of 168 Transplanted SCIDs by Molecular Type, 1982-2011: 151 had HLA Haplo-identical Donors, 17 Identical Donors, No Pre-Transplant Conditioning

Causes of Death in 40 SCIDs After Marrow Transplantation

- CMV 9
- Adenovirus 9
- EBV /Lymphoma 6
- Enterovirus, Rotovirus 4
- Parainfluenza 3, Varicella 4, 2
- Herpes simplex/RSV 1 ea
- Pulmonary disease 4
- Candida sepsis 2
- Mitochondrial defect 1
- CNS Infection 1
- Nephrotic syndrome/chemo 1
- VOD 1
- GVHD 0


Effect of Age at Transplant on Survival of 166 SCIDs Transplanted at Duke University Medical Center Since 1982
Percent Survival
100
90
80
70
60
50
40
30
20
10
0
0
50
100
150
200
250
300
350
400
450
500
550
600
Days of Age at time of Transplantation

Important Date

- January 2010, SACHDNC unanimously recommended adding SCID to conditions routinely screened for at birth.
- May 2010, HHS Secretary Sebelius adopted the Committee's recommendation to add SCID as a core condition, and related T cell lymphopenias as secondary conditions and endorsed both as a national standard.

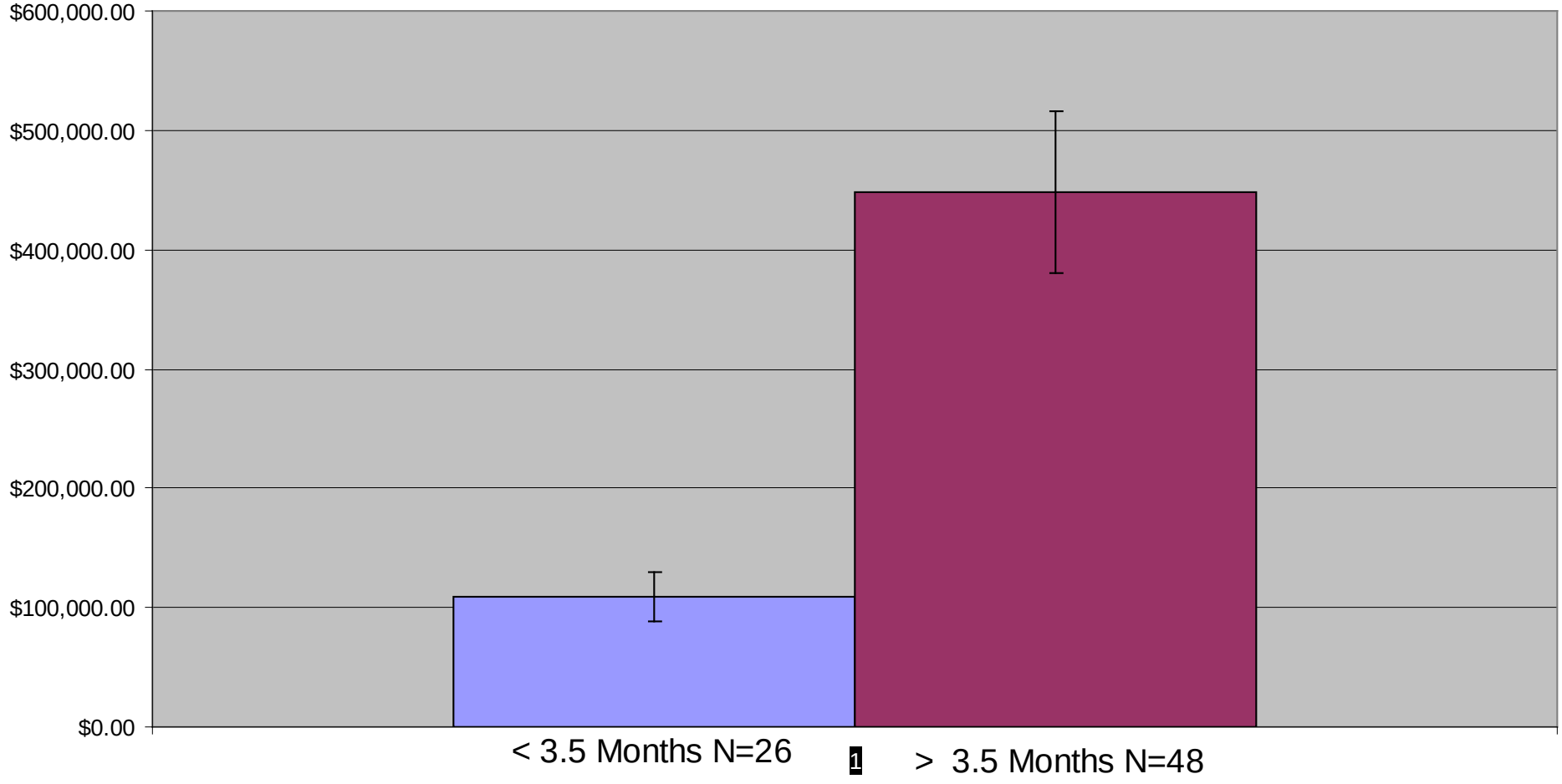
Advantages of Rigorously T-Cell-Depleted Haploidentical Non-Ablated Parental Marrow Transplants

- Donor usually always immediately available.
- Don’t have to wait for patient to get over infections or become stable.
- Can do in neonates.
- Can do essentially as an outpatient transplant if patient is well.
- Avoids the side effects of chemotherapy and GVHD prophylactic drugs.

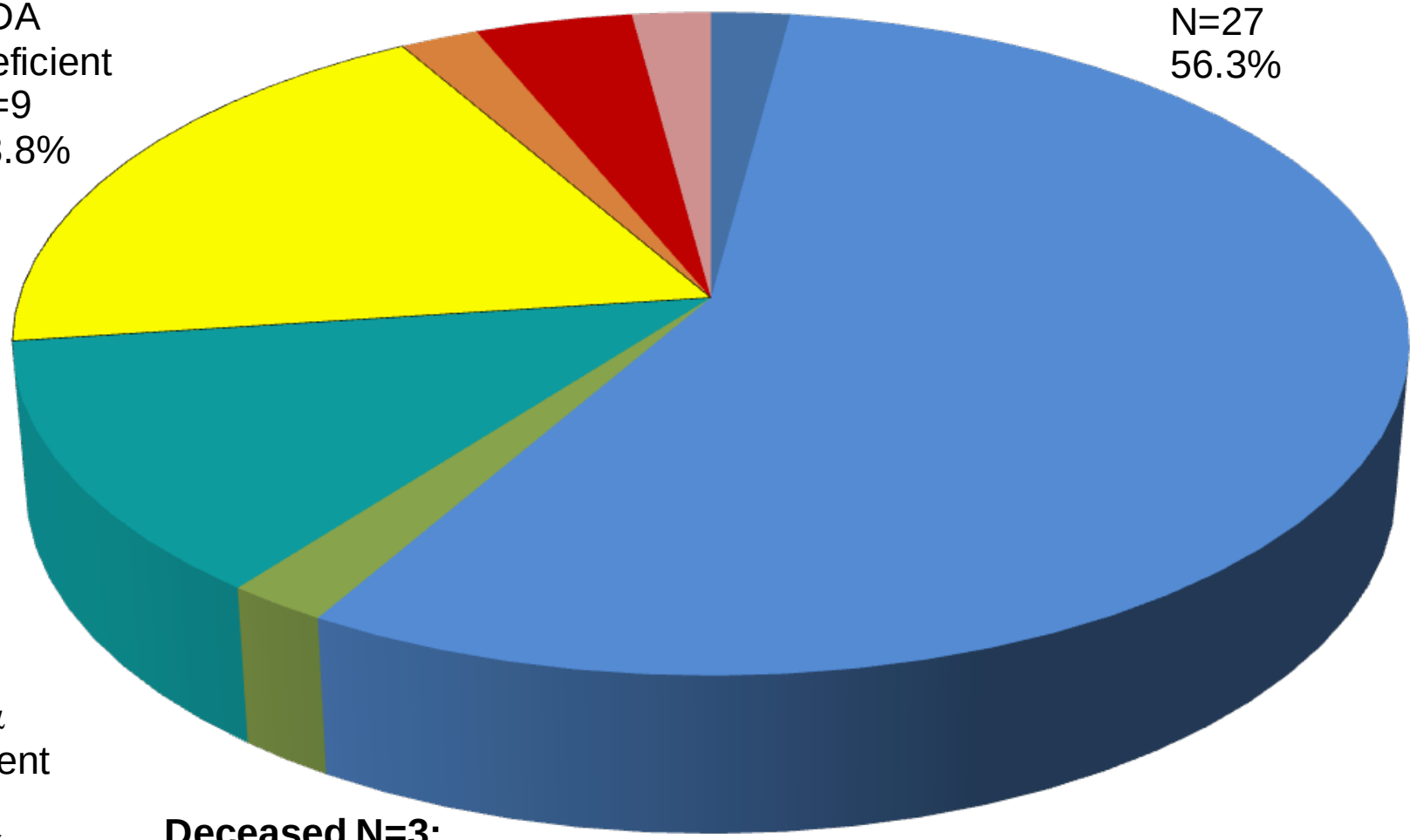
Neonatal Bone Marrow Transplants

- Of the 48 SCID infants transplanted early, 34 were neonates (i.e. less than a month of age), 12 of them were 10 days of age or less at transplant and 1 was a 31 week premie transplanted at 7 days of age. Donors were mothers (9), fathers (2) or siblings (1). None were infected at the time of transplant. None received pre-transplant chemotherapy.
- Except for the marrow cell infusion, the infants were outpatients. They were admitted overnight for the cell infusion, then discharged to an apartment and followed in the clinic every 1-2 weeks until T cell function developed. They did not have central lines or GVHD prophylaxis, and a majority were breastfed.

Mean Total Costs of SCID Bone Marrow Transplants According to Age of the Patient at Transplantation (N=74)



48 SCIDs Transplanted at Duke in the First 3.5 Months of Life: 5 HLA-identical, 43 Haploidentical, No Pre-Tx Chemo



Deceased N=3:
1 X-SCID
1 ADADef SCID
1 IL7Rα Def

Survivors:
N=45, 94%

Jak3=1, RAG=2, AutoRec=1,
CD3δ=1 Artemis=1

Survival Rates in SCIDs Transplanted Before 3.5 Months of Life

Authors	Location	Total # SCIDs	Overall Survival
Kane et al., 2001	Newcastle	13	100%
Myers et al., 2002	Duke	24	95%
Buckley et al., 2008	Duke	48	94%

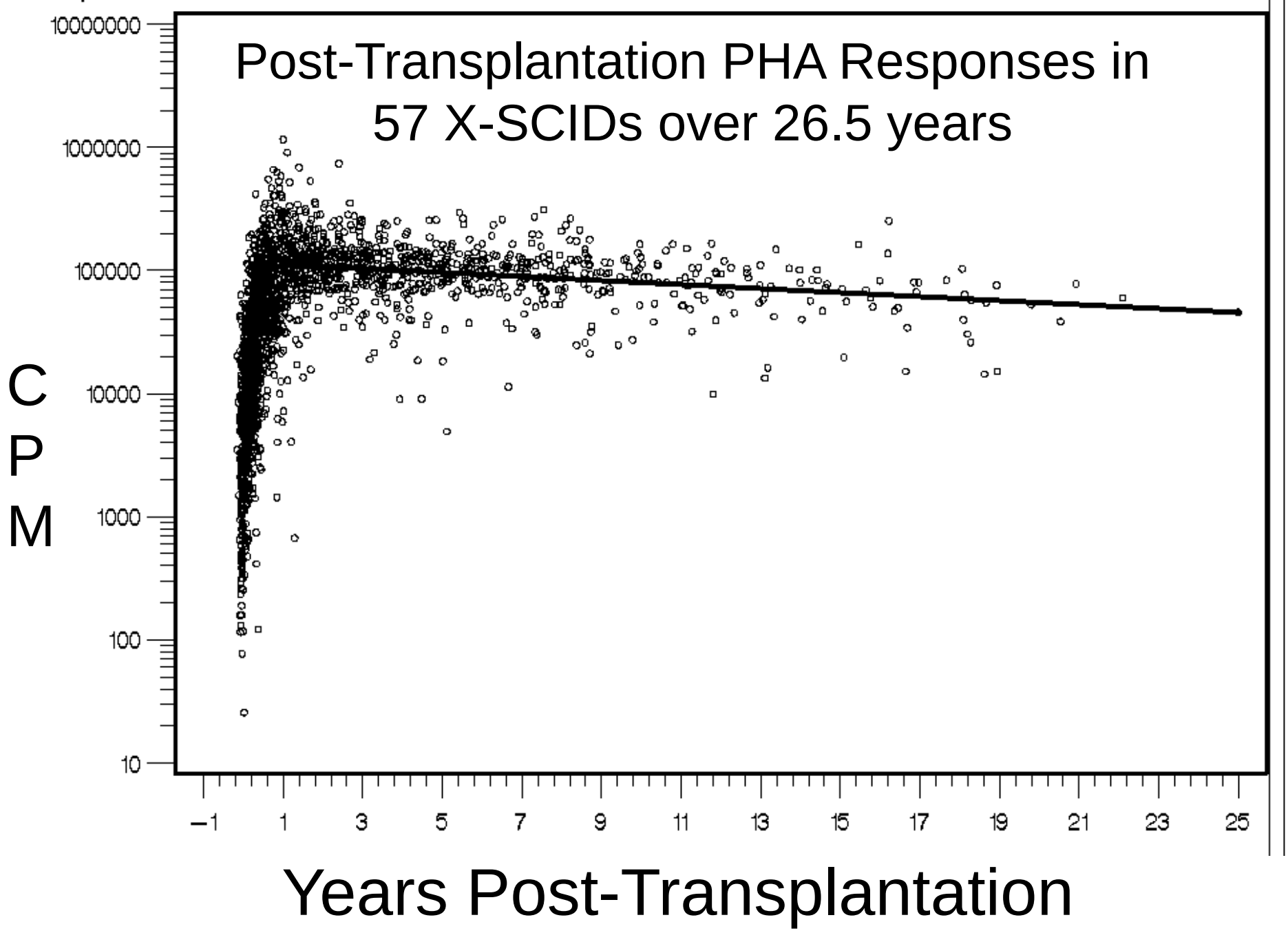
- Recent report by Brown et al, Blood 117: 3243-46,2011 of a retrospective study of 60 SCID patients diagnosed soon after birth because of a family history and transplanted at 2 UK centers showed that there was a 90% survival rate compared with 40% in the probands.

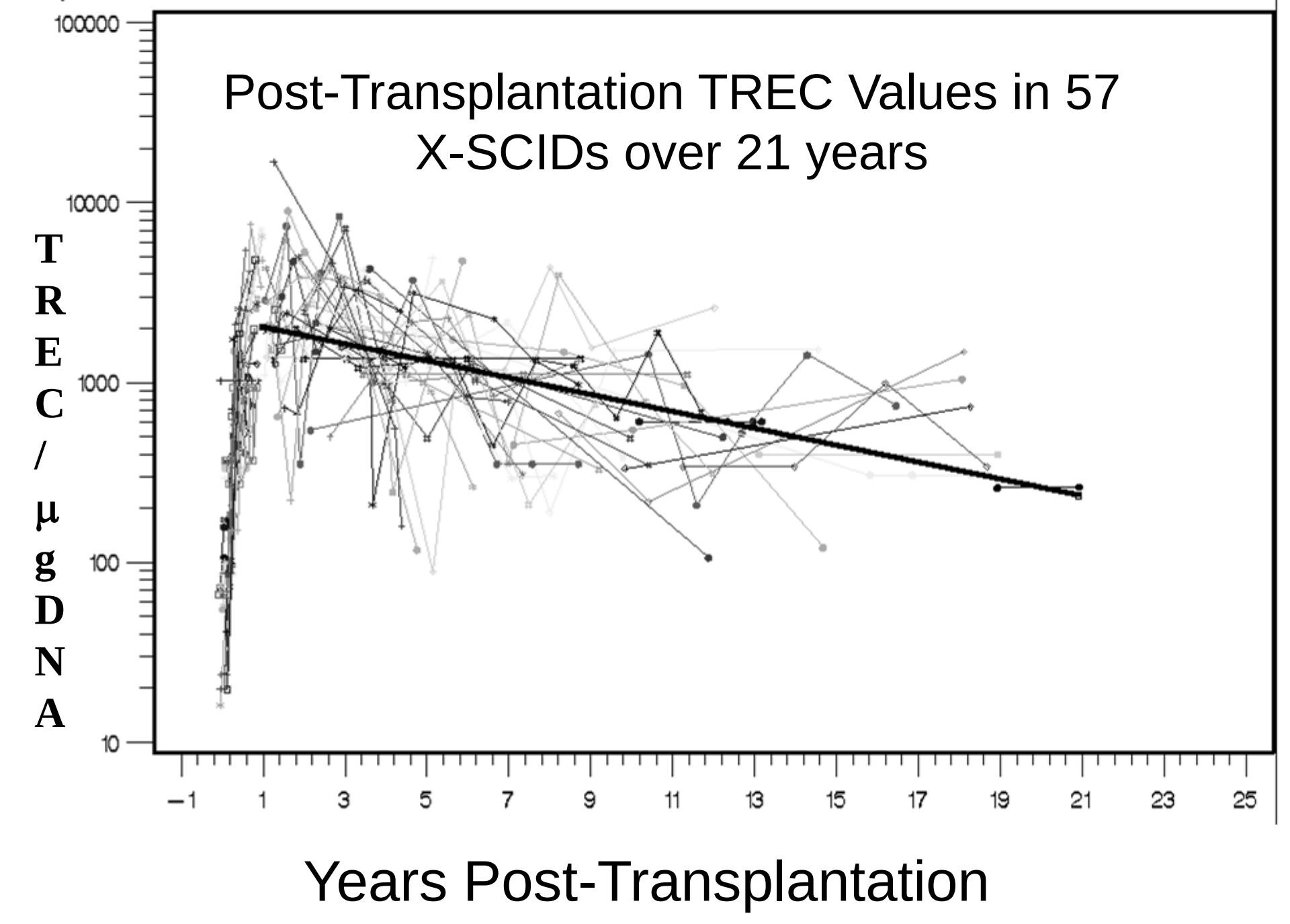
Survival Rates in SCID Transplants Regardless of Age at Transplantation

Authors	Location	Total # SCIDs	Overall Survival
Haddad et al. 1998	European Soc. ID	193	48%
Bertrand et al., 1999	European Soc. ID	178	52%
Smogorzewska et al.,2000	LA Childrens	48	58%
O'Marcaigh et al.2001	UCSF	16	75%
Buckley et al., 2008	Duke	162	77%

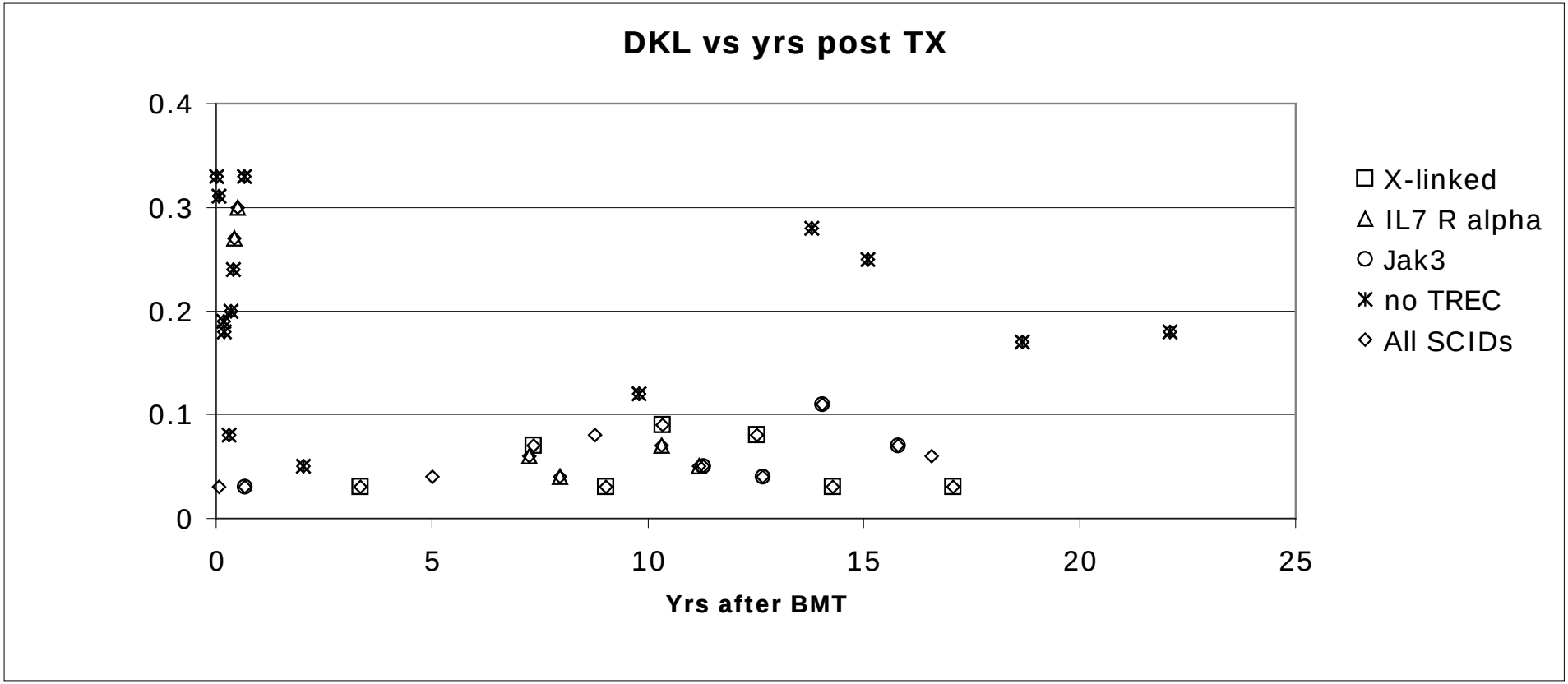
Published Longterm Outcomes of Gene Therapy in X-SCID

- Hacein-Bey-Abina,S. et al. NEJM 363: 355-364. 2010: 8/9 patients in French study surviving for up to 11 years. Transduced T cells found in all with good T cell diversity. No transduced B cells were found. Four had leukemia/lymphoma.
- Gaspar,H.B. et al. Sci Transl Med. 3: 97, 2011: 10 patients in English study surviving for up to 9 years. Transduced T cells found in all with good T cell diversity. No transduced B cells were found. One had leukemia.

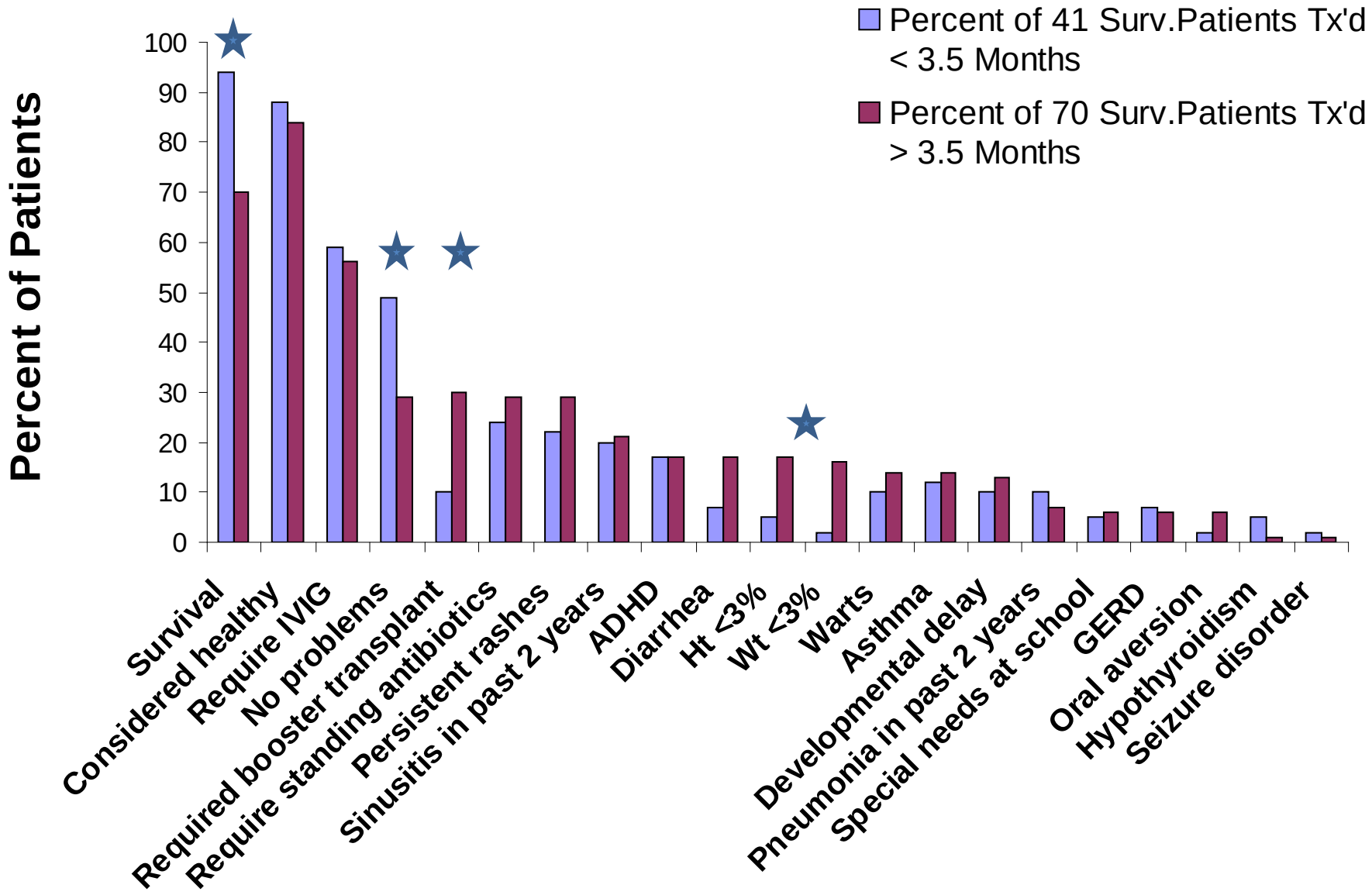

Post-Transplantation PHA Responses in 57 X-SCIDs over 26.5 years
C P M
10000000
1000000
100000
10000
1000
100
10
−1
1
3
5
7
9
11
13
15
17
19
21
23
25
Years Post-Transplantation


Post-Transplantation TREC Values in 57 X-SCIDs over 21 years
TREC/µgDNA
100000
10000
1000
100
10
−1
1
3
5
7
9
11
13
15
17
19
21
23
25
Years Post-Transplantation

T Cell Diversity by Spectratyping



Clinical Status Post-transplantation



? Advantages of Gene Therapy over T cell-depleted Haploidentical Transplants

- Originally reported that all lineages (B, T and NK) were transduced with IL2Rγ cDNA. That appears not to be the case longterm. Thus, no advantage for gene therapy.
- No need for a donor search. Same is true for haploidentical transplants. Usually always have at least one parent available and mothers are the best donors.
- No need for pre-transplant chemotherapy or post-transplant GVHD. Same is true for rigorously T cell-depleted haploidentical bone marrow transplants.
- Malignancy risk greater for gene therapy.

Conclusions

- SCID is a pediatric emergency, and the potential exists to diagnose this condition routinely at birth.
- If a rigorously T cell depleted stem cell transplant from a relative can be done in the first 3.5 months of life without pre-transplant chemotherapy or post-transplant GVHD prophylaxis, before infections develop, there is a high (94 percent) probability of success.
- Non-ablated T cell-depleted haploidentical marrow transplantation provides life-saving therapy for all forms of SCID, but it is not a perfect treatment.

Collaborators

Co-Investigators

- Joseph L. Roberts, MD/PhD
- Marcella Sarzotti-Kelsoe, PhD
- Dongfeng Chen, Ph.D.
- Michael Keller, MD
- Mary Dell Railey, M..D.

Duke Clinicians

- Wesley Burks, MD
- Brian Vickery, MD
- M. Louise Markert, MD/PhD
- Ivan Chinn, MD
- Paul Szabolcs, MD

Co-ordinators and Care

- Referring Physicians
- Debra Sedlak, CPNP
- A/I Fellows
- Pediatric Residents

Duke Technicians

- Roberta Parrott, BS
- Chan M. Win, BS
- Lily Daniel, BS
- Donna Oliver, MT

Graft-vs Host Disease

- Only 3/48 (6%) SCID infants transplanted in the first 3.5 months of life had GVHD >2+. Seven more had grade 1 GVHD, for an overall incidence of 21% any grade GVHD.
- All 3 with > 2+ GVHD still have some but very mild chronic cutaneous GVHD affecting their fingers and toes. They are doing well otherwise and have no other manifestation of GVHD. They are all teenagers now and are all well grown and healthy.
- No GVHD prophylactic immunosuppressive drugs were given any of these infants. The only measure taken to prevent GVHD was rigorous T cell depletion of the related donor marrow.